1,046,566

PATENT SPECIFICATION

DRAWINGS ATTACHED

1,046,566

Date of Application and filing Complete Specification: May 12, 1965.

No. 20087/65.

Application made in Japan (No. 26913) on May 14, 1964.

Application made in Japan (No. 48426) on Aug. 28, 1964.

Complete Specification Published: Oct. 26, 1966.

Index at acceptance:—C2 C(3A8A3, 3A8B2, 3A8C2, 3A8G1, 3A19A3, 3A19B2, 3A19C1, 3A19D1)

Int. Cl.:—C 07 c 171/04

COMPLETE SPECIFICATION

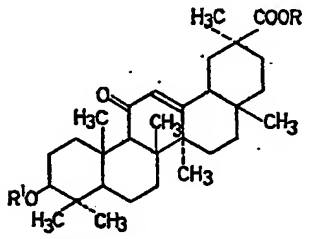
Glycyrrhetinic Acid Esters and the method of preparation thereof

We, MARUZEN KASEI CO., LTD., a Japanese body corporate of 14703—10, Mukaihigashi-cho, Mitsuki-gun, Hiroshima-ken, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel glycyrrhetinic acid esters and the methods of preparing thereof.

These compounds have a generic formula (I) such as follows:

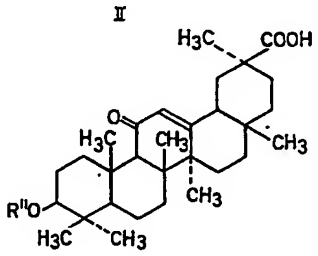
(I)



wherein R is a stearyl or oleyl group, and R' is hydrogen or a stearoyl or oleoyl group.

3-Alkanoyloxy glycyrrhetinic acid (II) bonded with an alkanoyl group of up to 4 carbon atoms and alkyl glycyrrhetinate (III) having an alkyl group of up to 4 carbon atoms have been reported up to this time.

II



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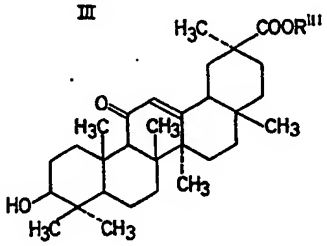


in which two foregoing formulas R'' is an alkanoyl group of not more than 4 carbon atoms and R''' is an alkyl group of not more than 4 carbon atoms in their respective formulas.

The anti-inflammatory effect of these compounds however is only equal to, if not less than, that of glycyrrhetinic acid.

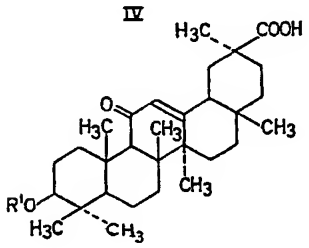
I found that the glycyrrhetinic acid esters of the present invention not only had an anti-inflammatory effect much superior to that of glycyrrhetinic acid, but also that it excelled in its solubility in fats as well as its solubility in organic solvents.

Thus, the product of this invention is suitable for use in oil preparations, salves, emulsions and sticklike preparations and exhibits excellent an anti-phlogistic effect because of its good transcutaneous absorption. This is a characteristic which was not noted in the known glycyrrhetinic acid and its esters and is an unexpected result.

Further, it was found that the invention product could be used for the same purpose as the corticoidal hormones. And in this case, a noteworthy characteristic of the invention product is the fact that side reactions such as were manifested in case of the corticoidal hormones, i.e., deposits of sugar and shrinkage of the adrenals, do not occur. In other words, the invention product has excellent uses as an anti-phlogistic agent because of its very low toxicity and absence of side reactions.

These compounds (I) of the present invention are prepared by reacting an oleyl or stearyl alcohol or halide with a compound having the following formula (IV):

IV



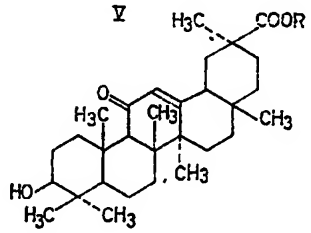
wherein R′ has the meaning hereinbefore defined.

For example, these compounds (I) are prepared by reacting stearyl or oleyl halide with the compound (IV) in the presence of an alkaline catalyst such as an alkali bicarbonate, alkali carbonate, organic amines or other alkaline substances.

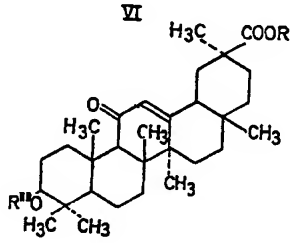
Further, the compounds (I) can also be obtained by reacting stearyl or oleyl alcohol with the compound (IV) in the presence of an acid esterification accelerator such as hydrochloric acid, sulfuric acid and aromatic sulfonic acids.

Further, a compound such as of the following formula (VI) [this compound is comprehended by the compound having the aforesaid formula (I)] can also be prepared by reacting a glycyrrhetinic acid ester having the following formula (V) with stearyl or oleyl halide.

V



VI



in which two foregoing formulas R has the meaning as hereinbefore defined and R′′′′ is a stearyl or oleoyl group.

The accompanying drawings are in all cases infrared spectrum curves, Figs. 1—4 being those of the invention compounds obtained in Examples 1—4, respectively, whereas Fig. 5 is that of glycyrrhetinic acid presented as a control.

The following examples are given to illustrate the invention further, it being understood however that these examples are not in limitation of the invention.

Example 1

Preparation of stearyl glycyrrhetinate.

A mixture of 2.35 g of glycyrrhetinic acid, 1.67 g of stearyl bromide and 0.5 g of potassium bicarbonate is heated under reflux for 10 hours in 30 cc of anhydrous ethanol. After completion of the reaction, the reaction mixture is filtered and concentrated. Then when the crystals deposited after cooling are recrystallized from anhydrous ethanol, 2.88 g of colorless, flaky crystals having a melting point of 116—118°C are obtained. The infrared absorption spectrum curve of these crystals are as shown in Fig. 1, and the elementary analysis results and calculated values (as $C_{48}H_{82}O_4$) are as follows:

Experimental values : C=79.72%, H=11.43%
Calculated values : C=79.58%, H=11.25%

EXAMPLE 2

Preparation of stearyl glycyrrhetinate.

Thirty cc of chloroform are added to 30 g of stearyl alcohol and dissolved. In this solution are suspended 4.7 g of glycyrrhetinic acid, followed by passing anhydrous hydrochloric acid gas therethrough for 4 hours. After allowing to stand overnight, the mixture is heated on a water bath and the hydrochloric acid gas and chloroform are distilled off. This is followed by distilling off of the excess stearyl alcohol on an oil bath at reduced pressure. When the residual product is recrystallized from ethanol, 2.6 g of colorless, flaky crystals having a melting point of 116—118°C are obtained.

The infrared absorption spectrum curve of these crystals are as shown in Fig. 2.

EXAMPLE 3

Preparation of oleyl glycyrrhetinate.

4.7 g of glycyrrhetinic acid are suspended in 20 cc of oleyl alcohol, following which anhydrous hydrochloric acid gas is passed therethrough for 2 hours. After allowing this suspension to stand overnight, it is heated on a water bath, followed by reducing the pressure to eliminate the hydrochloric acid gas. This is followed by heating over an oil bath at reduced pressure to distill off the excess oleyl alcohol to thereby obtain a jelly-like residual product. This product is, dissolved in benzene and, after purifying by passing through a column of alumina, the benzene is distilled off completely. The yield is 6.1 g.

The infrared absorption spectrum curve of this product is as shown in Fig. 3 and the results of an elementary analysis and calculated values are as follows:

Calculated values : C=79.29%, H=11.09%.
Experimental values : C=79.64%, H=10.88%.

EXAMPLE 4

Preparation of stearyl stearoyloxy glycyrrhetinate.

1.48 g of 3-stearoyloxy glycyrrhetinic acid are dissolved in 20 cc of anhydrous ethanol, following which 0.67 g of stearyl bromide and 0.15 g of anhydrous sodium carbonate are added. The mixture is then refluxed for 5 hours on a water bath. After completion of the reaction, the reaction mixture is filtered while hot and the filtrate is concentrated followed by addition of a small amount of water. The crystals deposited after cooling are separated by filtration. When these crystals are recrystallized from ethanol, 1.64 g of colorless crystals are obtained.

The infrared absorption spectrum curve of these crystals is as shown in Fig. 4, and the results of an elementary analysis and calculated values (as $C_{66}H_{118}O_5$) are as follows:

Calculated values : C=79.94%, H=11.99%
Experimental values : C=79.77%, H=11.86%

EXAMPLE 5

This example illustrates the pharmacological test of the invention chemical substances.

The materials of the experiment

The following compounds were used in the experiment.

(1) Stearyl glycyrrhetinate (a compound of formula (I) wherein the R and R′ therein are a stearyl group and hydrogen, respectively).
(2) Oleyl glycyrrhetinate (a compound of formula (I) wherein the R and R′ therein are an oleyl group and hydrogen, respectively).
(3) Stearyl 3-stearoyloxy-glycyrrhetinate (a compound of formula (I) wherein the R and R′ therein are stearyl group and a stearoyl group, respectively).
(4) 3-Acetoxy-glycyrrhetinic acid.
(5) 3-Lauroyloxy-glycyrrhetinic acid.
(6) 3-Palmitoyloxy-glycyrrhetinic acid.
(7) Lauryl glycyrrhetinate.
(8) Cetyl glycyrrhetinate.

The procedures of the experiment

Male rats of the Wistar weighing about 150 grams are administered by the hypodermic injection of glycyrrhetinic acid and the derivatives thereof daily for 7 successive days. The

dose administered is millimole/2 ml/kg as a 1% Tween (Registered Trade Mark) 80 sesame oil suspension.

The anti-inflammatory effect was tested by means of animal experiments using the following procedures.

(1) Rat foot test [H. Selye, Brit. Med. Jour. *2*, 1129 (1949)]

The test drug is injected hypodermically into rats daily for 7 days. On the last day, 0.1 ml of 10% solution of physiological saline in formalin is injected into the tendinous membrane of the sole of the back feet of the rats. The extent of the increase in the swelling of the feet after the lapse of 1, 2 and 3 hours are measured and the difference in the average value of the increase in the swelling of the feet between the treated and untreated rats are indicated as the rate of inhibition.

(2) The cotton pellet method [R. Meir et al., Experimented, *6*, 469 (1959)]

Four dental cotton pellets of about 5 mg are weighed and then each is transplanted to the axillae and inguinal regions of a rat, following which the rat is administered hypodermic injections for 7 successive days. The rat is killed, the cotton pellets removed, the excess tissue is cut away, and the pellets are dried overnight at 60°C. The pellets are scaled for their weights, and the difference between the weights before starting the experiment and the weights after completion is consider to be amount of the granular tissue. In this case, the statistical standard deviation is also calculated.

Results of the experiments

The results obtained in the rat foot and cotton pellet tests are shown in Tables I and II, respectively.

When the anti-inflammatory effect of the several compounds, as obtained by the rat foot test, is indicated by means of the inhibition rate, as is apparent from Table I, the following compounds have the rates as indicated below:

Stearyl glycyrrhetinate	37.5%
Oleyl glycrrhetinate	36.7%
Stearyl 3-stearoyloxy glycyrrhetinate	44%

When these are compared with the inhibition rate of glycyrrhetinic acid, letting 1.00 be the rate of the latter, the following ratios are obtained.

Stearyl glycyrrhetinate	2.3 times
Oleyl glycyrrhetinate	2.25 times
Stearyl 3-stearoyloxy-glycyrrhetinate	2.69 times

Next, when the anti-inflammatory effect of the several compounds, as obtained by the cotton pellet test, is indicated by means of the inhibition rate, as is apparent from Table II, the following compounds have the below-indicated rates.

Stearyl glycyrrhetinate	40.1%
Oleyl glycyrrhetinate	35.1%
Stearyl 3-stearoyloxy-glycyrrhetinate	43.2%

When these are compared with the inhibition rate of glycyrrhetinic acid, letting 1.00 be the rate of the latter, the following ratios are obtained.

Stearyl glycyrrhetinate	2.78 times
Oleyl glycyrrhetinate	2.44 times
Stearyl 3-stearoyloxy-glycyrrhetinate	3.00 times

TABLE I

No.	Drugs	Swelling of Foot		Inhibition rate	Inhibition ratio
		Increase	Difference of increase		
1	Control	2.75 ± 0.21	—	—	—
2	Glycyrrhetinic acid	2.30 ± 0.19	0.45 ± 0.03	16.3%	1.00
3	3-Acetoxy Glycyrrhetinic acid	2.42 ± 0.20	0.33 ± 0.02	12.0	0.73
4	3-Lauroyloxy Glycyrrhetinic acid	2.72 ± 0.17	0.03 ± 0.01	1.1	0.07
5	3-Palmitoyloxy Glycyrrhetinic acid	2.62 ± 0.22	0.15 ± 0.01	5.5	0.34
6	Lauryl Glycyrrhetinate	2.20 ± 0.16	0.55 ± 0.03	20.0	1.22
7	Cetyl Glycyrrhetinate	2.10±0.16	0.65 ± 0.04	23.6	1.44
8	Stearyl Glycyrrhetinate	1.72 ± 0.12	1.03 ± 0.09	37.5	2.30
9	Oleyl Glycyrrhetinate	1.74 ± 0.14	1.01 ± 0.09	36.7	2.25
10	Stearyl 3-Stearoyloxy-Glycyrrhetinate	1.54 ± 0.10	1.21 ± 0.10	44.0	2.69

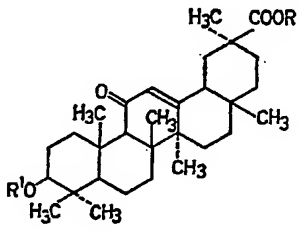
TABLE II

No.	Drugs	Weight of Cotton Pellet		Inhibition rate	Inhibition ratio
		Increase	Difference of increase		
1	Control	8.95 ± 0.72	—	—	—
2	Glycyrrhetinic acid	7.66 ± 0.71	1.29 ± 0.08	14.4%	1.00
3	3-Acetoxy Glycyrrhetinic acid	8.12 ± 0.70	0.83 ± 0.06	9.2	0.64
4	3-Lauroyloxy Glycyrrhetinic acid	8.52 ± 0.68	0.43 ± 0.03	4.7	0.33
5	3-Palmitoyloxy Glycyrrhetinic acid	8.47 ± 0.74	0.48 ± 0.03	5.3	0.37
6	Lauryl Glycyrrhetinate	7.26 ± 0.49	1.69 ± 0.11	18.8	1.31
7	Cetyl Glycyrrhetinate	7.10 ± 0.53	1.85 ± 0.09	20.6	1.43
8	Stearyl Glycyrrhetinate	5.36 ± 0.28	3.59 ± 0.29	40.1	2.78
9	Oleyl Glycyrrhetinate	5.80 ± 0.36	3.15 ± 0.21	35.1	2.44
10	Stearyl 3-Stearoyloxy-Glycyrrhetinate	5.08 ± 0.41	3.87 ± 0.31	43.2	3.00

As described above, the results of the rat foot test and the cotton pellet test show a similar tendency, it being shown that stearyl glycyrrhetinate, oleyl glycyrrhetinate and stearyl 3-stearoyloxy-glycyrrhetinate of the present invention, in all cases, have a much more potent anti-inflammatory effect than the reference compound glycyrrhetinic acid. The other compounds manifested results which were only equal to, if not less, than glycyrrhetinic acid. Hence, it can be said that the compounds of the present invention are novel anti-inflammatory agents whose effect is much more potent than the known glycyrrhetinic acid.

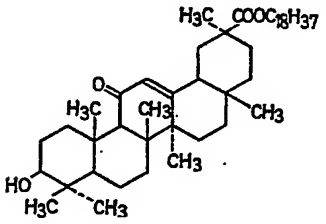
WHAT WE CLAIM IS:—

1. Glycyrrhetinic acid esters represented by the generic formula

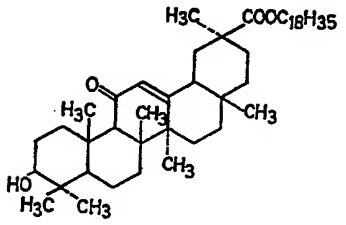


wherein R is a stearyl or oleyl group, and R' is hydrogen or a stearoyl or oleoyl group.

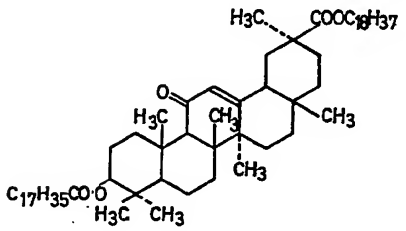
2. Stearyl glycyrrhetinate having the formula



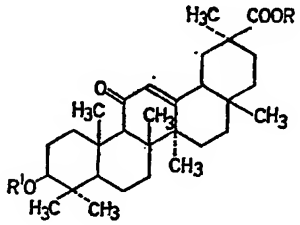
3. Oleyl glycyrrhetinate having the formula



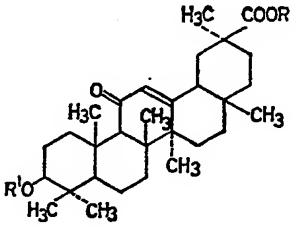
4. Stearyl 3 - Stearoyloxy - glycyrrhetinate having the formula



5. A method of preparing glycyrrhetinic acid esters represented by the generic formula



wherein R is a stearyl or oleyl group and R' is hydrogen or a stearoyl or oleoyl group, which comprises reacting in the presence of an alkaline catalyst a stearyl or oleyl halide with a compound represented by the generic formula



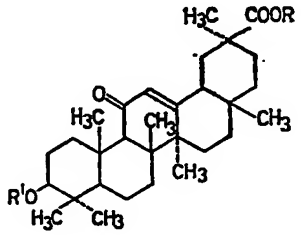
wherein R' has the meaning defined hereinabove.

6. A method of preparing stearyl glycyrrhetinate which comprises reacting glycyrrhetinic acid with a stearyl halide in the presence of an alkaline catalyst.

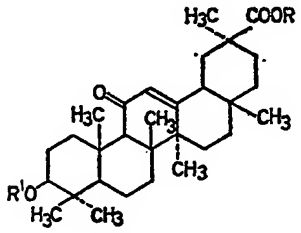
7. A method of preparing oleyl glycyrrhetinate which comprises reacting glycyrrhetinic acid with an oleyl halide in the presence of an alkaline catalyst.

8. A method of preparing stearyl 3-stearoyloxy-glycyrrhetinate which comprises reacting 3-stearoyloxy glycyrrhetinic acid with a stearyl halide in the presence of an alkaline catalyst.

9. A method of preparing glycyrrhetinic acid esters represented by the generic formula



wherein R is a stearyl or oleyl group, and R′ is hydrogen or a stearoyl or oleoyl group, which comprises reacting in the presence of an acid esterification accelerator stearyl or oleyl alcohol with a compound having the generic formula



wherein R′ has the meaning defined hereinabove.

10. A method of preparing stearyl glycyrrhetinate which comprises reacting glycyrrhetinic acid with stearyl alcohol in the presence of an acid esterification accelerator.

11. A method of preparing oleyl glycyrrhetinate which comprises reacting glycyrrhetinic acid with oleyl alcohol in the presence of an acid esterification accelerator.

12. A method of preparing stearyl 3-stearoyloxy-gycyrrhetinate which comprises reacting 3-stearoyloxy-glycyrrhetinic acid with stearyl alcohol in the presence of an acid accelerator.

13. A method of preparing stearyl 3-stearoyloxy-glycyrrhetinate which comprises reacting stearyl glycyrrhetinate with a stearoyl halide.

14. A method of preparing a glycyrrhetinic acid ester as defined in claim 1 substantially as hereinbefore described.

15. A method of preparing a glycyrrhetinic acid ester substantially as described in any of Examples 1 to 4.

16. A glycyrrhetinic acid ester whenever prepared by the method of any one of claims 5 to 15.

17. A pharmaceutical composition comprising as active ingredient a glycyrrhetinic acid ester as defined in any one of claims 1 to 4 and 16 together with an inert carrier.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

Fig. 1

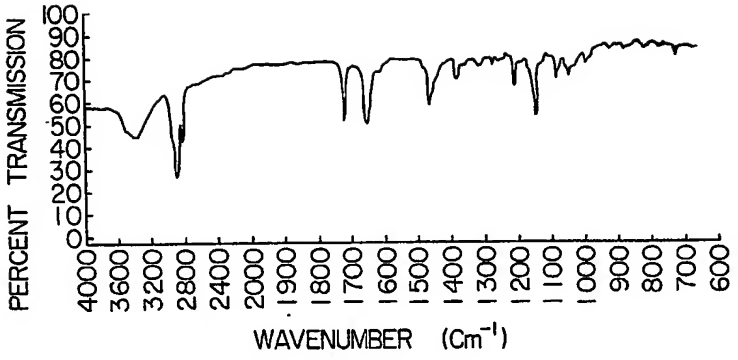
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Fig. 2

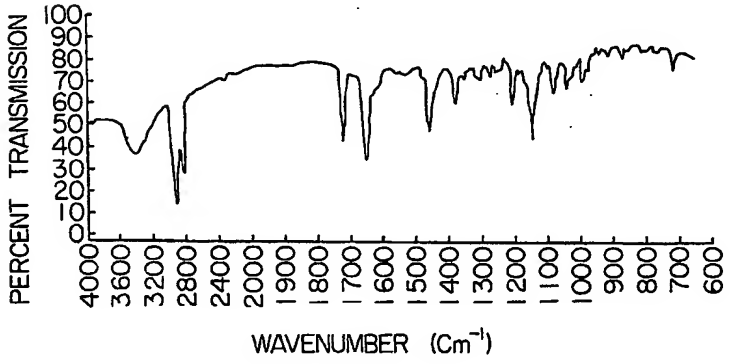
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Fig. 3

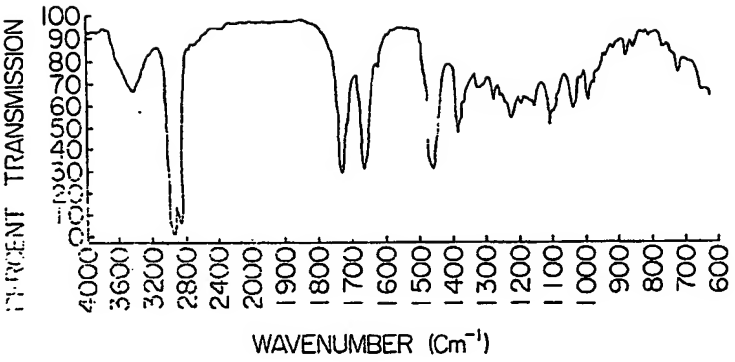
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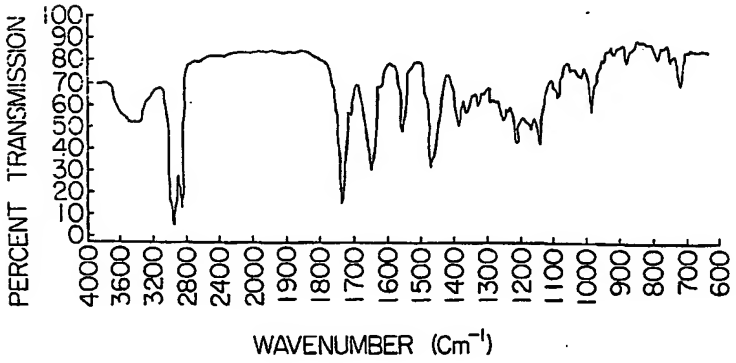
Fig. 4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1046566 COMPLETE SPECIFICATION

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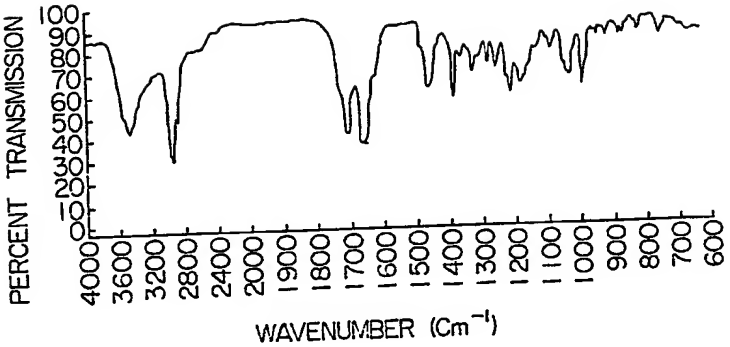
Fig. 5



1046566 COMPLETE SPECIFICATION
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Sheets 2 & 3

Fig. 3

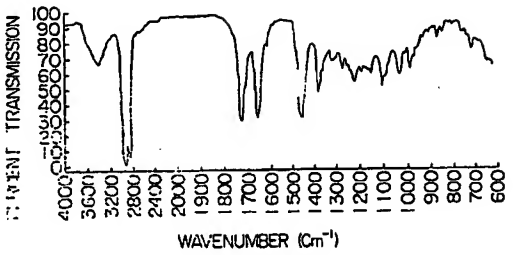

Fig. 4

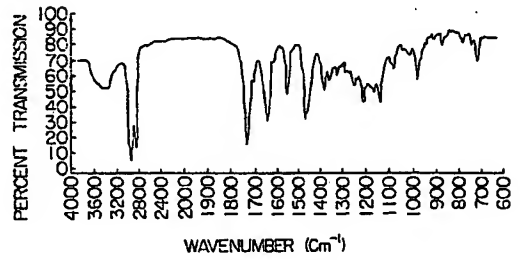

Fig. 5